REMARKS

Claims 1-3 and 7-14 are currently pending in the present application. Claims 1 and 13 have been amended herein, as will be discussed fully below. Applicants submit that no new matter has been added by way of the present claim amendments.

35 U.S.C. 112, First Paragraph

Claims 1, 2 and 7-13 stand rejected as failing to satisfy the written description requirement.

The present claims have been amended to clarify that the desired outcome of the method is the identification of heterologous DNA sequences that cause an electrophysiological change (of any magnitude) in a cell. This is described in the specification, at least, at page 2, lines 13-14 and 20-22. This outcome is the same irrespective of the cell type or the heterologous DNA, and accordingly is what distinguishes the cell and DNA of interest from those cells exhibiting no change in electrophysiology.

The change in electrophysiology of the cell containing heterologous DNA in comparison to a control cell (step (iii) of the method of claim 1) is a characteristic that both distinguishes and identifies those cells of interest and that a change in electrophysiology can be measured in any cell type containing any heterologous DNA from a DNA library. This is described in the specification, at least, at page 4, line 28 – page 5, line 24.

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary

skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

The measurement of electrophysiological changes and differences is well within the skill of the art and is described in many electrophysiology texts. Moreover, as noted above, the relationship between electrophysiological change and the expression of heterologous DNA sequence is described in the present specification. Thus, Applicants have met the burden of conveying, with reasonable clarity, possession of the claimed invention to those of ordinary skill in the art.

Claims 1, 2 and 7-13 stand rejected as failing to comply with the enablement requirement.

Applicants respectfully submit that the Examiner appears to have misunderstood the claimed invention. The Examiner appears to believe that the gist of the claimed method is intended to find a specific magnitude of change in electrophysiology due to a specific heterologous DNA in a specific host cell.

However, the invention is actually a high-throughput screening method for studying whether the expression of a DNA sequence derived from a DNA library causes an electrophysiological change of any size in a host cell.

The electrophysiological method of the invention is intended as a screening method for identifying DNA sequences that influence electrophysiology. The invention is intended to be used with any DNA libraries, which may include any nucleotide sequences, and with any suitable host cells. The selection of DNA libraries for study would depend on which libraries were available to the skilled person and on which sequences were of interest to the skilled person performing the claimed method. Such a selection would be part of the daily routine of the skilled person who would most likely already be working on the same DNA libraries in other experimental procedures and therefore would be merely applying a new investigatory method to a DNA library they are already working with.

Furthermore, it is within the existing knowledge of a person of ordinary skill in the art, as to which DNA libraries will be expressed well in which host cells. Most likely the DNA library to be tested will either be a commercially available library that would be purchased, so as to include recommendations for suitable host cells, or the library would have been created by the skilled person who would be aware of which cells that library would be expressed in, through testing with methods such as western blotting or ELISA.

The skilled person using this invention would not create a library from scratch and run the claimed method of electrophysiological tests without first having tested the viability of the library to be expressed in at least one cell type. Therefore, the ability of a particular library to be expressed in a particular host cell would already be known and it would not require undue experimentation for the skilled person to perform the claimed method.

The phenotypic changes in the cell would be readily measurable, as they are demonstrated using the electrophysiology methods-- a change of electrophysiology of a test cell

in comparison to a control cell represents a phenotypic change (as discussed on page 5 of the specification). The Examiner has suggested that no direction is provided on how to measure the electrophysiological changes. However, Example 2 describes a suitable chip for performing the electrophysiological methods and Example 3 provides details of how the electrophysiological measurements are taken. A person of ordinary skill in the art who intended to carry out electrophysiology measurements of cells would be familiar with how to work a patch clamp and 2-electrode voltage clamp apparatus and therefore would easily be able to use the patch clamp chip described in Examples 2 and 3.

The identification of test agents to which the test cells can be exposed include any agent that may be of interest to the skilled person performing the method. The skilled person could readily select agents of interest that he wished to test whether they had an effect on the electrophysiology of a cell containing a heterologous DNA sequence. The specification provides guidance on page 4 that the test agent can be either intra- or extra- cellular and that possible examples of such test agents are small organic molecules, small peptides, neurotransmitters, hormones and cytokines.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable?

"[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "

35 U.S.C. 112, Second Paragraph

Claims 1, 2 and 7-13 stand rejected as being indefinite for failing to particularly point out and distinctly claim the invention. Applicants respectfully traverse.

Claim 1

The Examiner states it is unclear how the heterologous DNA is "derived" from a DNA library. While not acquiescing to the Examiner's rejection, in order to expedite prosecution, Applicants have amended claim 1 to replace "derived from" with the phrase "said DNA sequence being a member of'. A person of ordinary skill in the art would understand that DNA derived from a DNA library is a DNA molecule that is a member of that library. The present amendment should clarify this interpretation.

The Examiner further states that it is not clear how arrangement of cells on the substrate (step (iii) of claim I) permits detection of electrophysiology of the cell.

However, the substrate upon which the cells are arranged is defined in step (i) as being a substrate for making electrophysiological measurements, which is further made clear when read in light of the specification. The Examiner is tasked with determining the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "*in light of the specification as it would be interpreted by one of*

ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004) (Emphasis added). The substrate of the invention is the apparatus upon which the electrophysiological measurements are carried out. The specification demonstrates that the substrate can be a chip apparatus as described in Examples 2 and 3 (and figure 3) suitable for patch clamp measurements. Electrophysiology apparatuses can differ in composition and exact construction dependent on the model and manufacturer, however it is clear to the skilled person that the apparatus is used for making electrophysiological measurements. Therefore, it is clear that the substrate is the electrophysiology apparatus.

The Examiner further states that it is unclear how the differentiating characteristic of the cell of interest is determined (step (iv) of claim 1). Applicants assume that by "differentiating characteristic" of step (iv) the Examiner is referring to the "phenotypic change."

The phenotypic change recited in the claims is clearly defined on page 5 as being an electrophysiological change. However, solely in order to expedite prosecution, Applicants have amended claim 1 to replace the phrase "at least one phenotypic change" with the phrase "a change in the electrophysiology as measured in step (iii)". This amendment clarifies how the distinguishing feature is measured by reference back to a previous step.

The Examiner further states that it is not clear whether identification of the cell of interest is part of the method of measurement or a separate step.

The process of identifying the cells of interest is done by reviewing the electrophysiology data resulting from the method of step (iii). The analysis of such results is preferably conducted

while the cells are still located within the electrophysiology apparatus so that the isolation of mRNA is extracted and analyzed from only cells exhibiting a phenotypic change. However, the analysis may also be conducted as a separate step from the production of data showing any electrophysiological changes.

The Examiner further states that it is not clear what the relationship between the preamble and the rest of the claim is because the preamble refers to a method of conducting electrophysiological measurements but the outcome of the method steps is the identification of cells comprising heterologous DNA of interest.

Applicants have amended the preamble of claim 1 to recite: "A method for identifying heterologous DNA which causes, on its expression, an electrophysiological change in a cell". This amendment should overcome the rejection as it now provides a nexus between the preamble and the steps of the claimed method.

The Examiner further states that it is not clear what the relationship is between the cell of interest referred to in step (iv) and the method of step (iii).

Applicants have amended step (iv) to specify that the cell of interest is one that shows "a change in the electrophysiology as measured in step (iii) ". This amendment should clarify the link between the method of step (ii) and the cell of interest being identified in step (iv).

Claim 2

The Examiner states that claim 2 is indefinite because claim 1 already recites a sequenced genetic material.

However, claim 1 does not specifically recite a sequenced DNA molecule, merely a DNA sequence that is a member of a DNA library. A person of ordinary skill using a DNA library may not be in possession of the sequence information of every DNA molecule in that library.

In any event, when analyzing multiple cells each with a different heterologous DNA sequence from a DNA library, it is necessary to identify the specific DNA library member that is in a cell that produces a positive hit (i.e., a change in electrophysiology of the cell). The identity of a DNA sequence may not be immediately apparent when studying a large number of cells simultaneously or in quick succession. The most appropriate way to identify the particular DNA library member causing that change is to isolate it and sequence it. Accordingly, the step of sequencing the mRNA is a preferred, but not essential, method of determining which DNA library member is causing a change in electrophysiology.

Claims 9 and 10

The Examiner states that it is not clear why treating a cell with a test agent is essential.

The purpose of exposing the cell that comprises a heterologous DNA to a test agent is so that the effect of the test agent on the electrophysiology of the cell can be studied. For example, one possible scenario would be where an ion channel blocker is given as a test compound where the heterologous DNA is thought to be an ion channel. If exposure to the ion channel blocker altered the electrophysiological change due to the heterologous DNA, it could then assist in identification of the heterologous DNA as a particular ion channel type. Furthermore, exposure of the cells to certain ion channel blockers can be used to distinguish the effect of ion channels from background noise and baseline effects.

Accordingly, the process of the present claims can be used to both identify the function of a heterologous DNA and also in identifying possible drugs that may be useful as pharmaceuticals.

Claim 13

The Examiner states that it is not clear what the term "spaced apart" is intended to cover as there is no measure of distance given.

A person of ordinary skill in the art would understand the term to mean that the sites at which cells are located are not the same location and are distributed across the substrate.

The Examiner further states that it is not clear how in or on the substrate differs. Applicants have amended claim 13 to simply read "on the substrate".

Applicants submit that each of the Examiner's concerns has been fully addressed herein. Thus, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

35 U.S.C. 102

The Examiner has objected the pending claims are not novel in light of three cited documents: Qin (US 6994993) Gillespie (US 6936457) Maher (US 6969449). Applicants respectfully traverse.

Qin describes cells being transfected with cDNA or mRNA molecules encoding a Sodium gated ß1A subunit and the subsequent measurement of biological activity using electrophysiological techniques including in response to a test agent.

Gillespie describes patch clamp and 2 electrode-voltage clamp experiments on cells transfected with the neuronal nicotinic acetylcholine receptor.

Maher describes multiwell electrode assemblies that can be used to study cells transfected with the DNA/mRNA encoding an ion channel and the subsequent analysis of the electrophysiological profile of the ion channel being studied.

None of the three cited documents describe the analysis of multiple different DNA molecules as part of the same assembly. Each of these documents describes the analysis of cells (either singly or multiple cells) each containing the same heterologous DNA expressing a single defined ion channel. Claim 1 of this application requires that a plurality of cells, each containing a different heterologous DNA, that is a member of a DNA library.

The presently claimed invention differs from the prior art because the cited prior art does not describe the subsequent isolation of mRNA only from cells exhibiting some form of electrophysiological phenotypic change.

Moreover, the present claims are non-obvious over the cited documents because each of the cited documents only describe the study of a single ion channel deriving from one heterologous DNA molecule. There is no suggestion to study multiple different proteins expressed from multiple heterologous proteins.

As such, Applicants submit that the presently claimed invention is both novel and unobvious in view of the disclosures of Qin, Gillespie and Maher. Reconsideration and withdrawal of the outstanding rejections is respectfully requested.

In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

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